### THESIS TITLE

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<th>Thesis title:</th>
<th>Feces-derived extracellular vesicles from patients with liver diseases: characterization and bioactions</th>
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### Unit / team: INSERM U1063 SOPAM

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### Socio-economic and scientific context (approximately 10 lines):

Liver diseases, such as nonalcoholic fatty liver disease (NAFLD) can progress to non-alcoholic steatohepatitis (NASH) and fibrosis, and have been described as the hepatic manifestation of metabolic syndrome (MetS). Gut microbiota alterations influence multiple host metabolic responses and have been associated with the progression of NAFLD to NASH and fibrosis and lead to barrier dysfunctions including epithelial, endothelial and hepatic. Extracellular vesicles (EVs), small vesicles released from activated or apoptotic cells, are potential biomarkers and biological vectors of barrier dysfunctions associated with liver diseases. They can originate either from blood cells or from the feces including microbiota. We demonstrated that circulating EVs participate in both initiation and development of atherogenic process in MetS patients. Gut microbiota-derived EVs are able to reach the circulation and actively participate in the development of insulin resistance in experimental models of obesity. Based on our results, feces EVs from NAFLD and NASH patients display heterogeneity in levels and protein contents, and they induce differential effects on epithelial and endothelial cells and hepatocytes. Thus, EVs from feces can be explored as biomarkers allowing the discovery of novel targets involved in liver diseases.

### Working hypothesis and aims (approximately 8 lines):

The objectives of the study are to provide the characterization of EVs from feces with regard to cellular sources and contents, and to analyse their bioactions in order to predict the occurrence and the progression of liver diseases from NAFLD, NASH to fibrosis. The focus will be the common downstream consequences of liver diseases associated with epithelial, endothelial and hepatic dysfunctions and inflammation in the course of hepatic insults. The goal is to translate the knowledge on feces EVs to the bedside in order to improve the management and treatment of patients with liver diseases.

### Main milestones of the thesis (approximately 12 lines):

- Feces and blood from the SNIFF cohort of Hepatology department of CHU of Angers will be collected for EV extraction. Patients with simple steatosis, NASH with no/mild fibrosis, NASH with advanced fibrosis will be included.
- EV detection, characterization and sorting subsets. Established standardized protocols based in serial centrifugations to isolate, quantify and analyze EVs will be assessed. Nanoparticle tracking analysis for measurement of particle concentrations and size distribution, ELISA Western blot and electron microscopy for EV subpopulations will be conducted.
- We will determine whether feces EVs are the link between alteration of gut epithelial, hepatocyte and endothelial barrier functions, and inflammation and the development of liver injury from NAFLD to NASH in these patients. Based on our metagenomic data of EVs, we will select bacterial species of interest to demonstrate their potential involvement. We will verify the effects of in vivo EVs on intestinal barrier and liver functions from ApoE-/- mice fed with normal or high-fat diet in order to simulate liver alterations described in NAFLD and NASH patients. EVs will be orally administered. Intestinal permeability to fluorescein sulfonic acid and horseradish peroxidase and Western blot of tight junction proteins will be conducted. Mouse liver histology will be conducted by haematoxylin-eosin-saffron or picrosirius red solution. qPCR and ELISA will measure gene expression of inflammatory genes.

### Scientific and technical skills required by the candidate (2 lines):

**Cellular Biology, Molecular biology, Imaging and animal experimentation skills.**

### 3 publications from the team related to the topic (last 5 years):


### National and international collaborations:

**Michel Neunlist TENS Nantes, Miguel Lopez CIMUS Santiago de Compostela Spain**